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An alkylpolyglucoside surfactant as a prospective pharmaceutical excipient for topical formulations: The influence of oil polarity on the colloidal structure and hydrocortisone in vitro/in vivo permeation

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ABSTRACT

There is a growing need for research into new skin- and environment-friendly surfactants. This paper focuses on a natural surfactant of an alkylpolyglucoside type, which can form both thermotropic and lyotropic liquid-crystalline phases. The aim of this study was to relate some physicochemical properties (characterised by polarisation and transmission electron microscopy, thermal analysis and rheology) of the three formulations based on cetearyl glucoside and cetearyl alcohol, to the results of in vitro and in vivo bioavailability of hydrocortisone (HC). The three formulations contained oils of different polarity (medium chain triglycerides: MG, isopropyl myristate: IPM and light liquid paraffin: LP), respectively. In vitro permeation was followed through the artificial skin constructs (ASC), while the parameters measured in vivo were erythema index: EI (using instrumental human skin blanching assay), transepidermal water loss (TEWL) and stratum corneum hydration (SCH). The vehicles based on cetearyl glucoside and cetearyl alcohol showed a complex colloidal structure of lamellar liquid-crystalline and lamellar gel-crystalline type, depending on oil polarity. Rheological profile of the vehicle was directly related to the in vitro profile of the HC permeation. In vivo results suggested that the vehicle with MG retarded the HC permeation, whereas less polar IPM and non-polar LP enhanced it. It is suggested that the enhancement is achieved either by a direct interaction with lipid lamellae of the SC or indirectly by improving skin hydration.

There were no adverse effects during in vivo study, which indicates a good safety profile of this alkylpolyglucoside surfactant.

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1. Introduction

An increased attention to the environment over the past decade has produced a growing interest in the field of natural surfactants. The term "natural surfactant" relates in its broadest sense to the surface-active substance coming from natural raw materials. It includes a group of alkylpolyglucosides, which are derived from a natural sugar unit and a natural or non-natural fatty alcohol (Stubenrauch, 2001). Allegedly mild for the skin, with a large number of hydroxyl groups capable of providing additional skin hydration, these surfactants are highly recommended for formulations intended for topical application (Mehling and Hensen, 2004).

Given a significant increase in dermatological ailments related to the skin barrier impairment and their impact on quality of life, there is a growing need for new, safe and effective pharmaceutical excipients (cf. Hadgraft, 2004). It is well known that the vehicle is not inert and that in some cases could have a negative effect. For example, the anti-inflammatory effect of low-potency topical corticosteroids could be diminished by the choice of vehicles (Lehmann et al., 2001). Therefore, overcoming the problem of vehicle irritancy is an important formulation task, which may be fulfilled by adequate selection of emulsifiers (Bárány et al., 2000; Williams and Barry, 2004).

In addition to the role of stabilizers in topical preparations, a number of surfactants of pharmacopoeial quality, either ionic or polyethoxylated non-ionic, may improve drug penetration, but this is frequently accompanied by cutaneous adverse reactions (Williams and Barry, 2004). On the other hand, it is well established that increased permeability of the stratum corneum (SC) may be achieved by increasing the water content of this tissue. Of all the methods for enhancing the penetration of corticosteroids, an increased skin hydration via reduced transepidermal water loss causes the smallest toxicity or irritancy under normal circumstances (Zhai and Maibach, 2001; Williams and Barry, 2004).

Vehicles may affect the skin moisture content either through an occlusive effect of their lipid ingredients, or by controlling the mode of water distribution within the system. The latter is dependent on the colloidal structure of the vehicle, and could be enhanced by increasing the interlamellarly fixed water, which may serve as a formulation reservoir ("depot") for controlled skin hydration (Junginger, 1997). Such a structure may be reached thank to the mesomorphic behaviour of alkylpolyglucosides and it affects the properties important for dermatological use (physical stability, water distribution mode and rheological performance) (Savić et al., 2005; Savić et al., 2006).

In order for a new surfactant to be considered a reliable pharmaceutical excipient for topical products, a number of critical data is required, including a comprehensive physicochemical characterization in a variety of different formulations, a study of vehicle's impact on drug in vitro release/permeation and in vivo efficacy, and a safety evaluation. In a previous study, we have presented a detailed physicochemical characterization of the binary mixtures and multiphase emulsions stabilized with an alkylpolyglucoside mixed emulsifier (cetearyl glucoside and cetearyl alcohol), with medium chain triglycerides (MG) as oil phase (Savić et al., 2005). Furthermore, we have compared in vitro/in vivo permeation profiles of hydrocortisone (HC) from the two vehicles: an alkylpolyglucoside-based vehicle containing MG as an oil phase and a pharmacopoeial formulation (Savić et al., 2006). It was intriguing to investigate further how oil polarity affects the colloidal structure of vehicles based on this surfactant and whether or not it affects the in vitro and in vivo fate of HC. Three different oils of pharmacopoeial quality were used in fixed concentration (20%, w/w): MG, isopropyl myristate (IPM) and light liquid paraffin (LP), with polarity indexes (mN/m) 21.3, 24.2 and 43.7, respectively. Therefore, the present study aimed to relate the physicochemical properties of three different cetearyl glucoside and cetearyl alcohol-based formulations (especially the water distribution mode and rheological behaviour) with in vitro HC (1%, w/w) permeation through the human reconstructed skin model and in vivo study using the skin bioengineering methods. The parameters evaluated prior and upon 24 h treatment under occlusion were: SC hydration (SCH) and transepidermal water loss (TEWL), as a measure of skin barrier properties, and skin erythema index (EI), which indicates the pharmacodynamic response to a corticosteroid - skin blanching assay (Lehmann et al., 2001; Levin and Maibach, 2005).

2. Materials and methods

2.1. Materials

The alkylpolyglucoside non-ionic emulsifier cetearyl glucoside and cetearyl alcohol (Montanov™ 68 PHA, kindly provided by Seppic, France) was used in a fixed concentration of 7% (w/w) for the preparation of three model creams, labelled as follows: PL-MG, with medium chain triglycerides (Miglyol® 812, Hüls, Germany); PL-IPM with isopropyl myristate and PL-LP with light liquid paraffin. All samples contained 20% (w/w) of oil phase, each being of pharmacopoeial quality. The samples, preserved with 0.5% (w/w) Euxyl® K 300, (Schülke&Mayr, Germany), were prepared with double distilled water.

Active samples (MG-HC, IPM-HC and LP-HC) contained 1% (w/w) of micronized hydrocortisone, HC (Synopharm, Germany), as a model drug. All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Preparation of samples

A series of cream vehicles (placebo samples) with a fixed ratio of emulsifier/water (8.75:91.25, i.e. 1:10.43) and 20% (w/w) of oil phase (MG, IPM or LP) was prepared. For this purpose emulsifier and oil were heated together at 70 °C, and then added to the preserved water phase at the same temperature, using the mixing procedure previously described (Savić et al., 2005). Prepared samples were stored for a week prior to the physicochemical characterization.

In order to obtain homogeneous distribution, HC was suspended in emulsion vehicles, using the stirrer Unguator® (GAKO, Germany) at 1000 rpm for 2 min at the room tempera-